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Clinical Trial Results

Phase II Trial of Abiraterone Acetate Plus Prednisone in Black Men With Metastatic Prostate Cancer

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Trial Information

- **ClinicalTrials.gov Identifier:** NCT01735396
- **Sponsor:** Janssen Biotech
- **Principal Investigator:** Matthew David Galsky
- **IRB Approved:** Yes

Lessons Learned

- The safety and activity findings of abiraterone acetate plus prednisone treatment in black men with mCRPC were similar to results from previously conducted studies with largely white populations.
- Poor trial accrual continues to be a challenge in black men with mCRPC and further efforts are needed to address such underrepresentation.

Abstract

Background. Self-identified black men have higher incidence and mortality from prostate cancer in the United States compared with white men but are dramatically underrepresented in clinical trials exploring novel therapies for metastatic castration-resistant prostate cancer (mCRPC).

Methods. Black men with mCRPC were treated with abiraterone acetate (AA), 1,000 mg daily, and prednisone (P), 5 mg twice daily. The primary objective was to determine antitumor activity (defined by a ≥30% decline in prostate-specific antigen [PSA] level) and to correlate germline polymorphisms in androgen metabolism genes with antitumor activity. Secondary objectives included determining safety, post-treatment changes in measurable disease, and time to disease progression.

Results. From April 2013 to March 2016, a total of 11 black men were enrolled and received AA plus P (AA+P); 7 of 10 evaluable patients were docetaxel naive. Post-treatment declines in PSA level of ≥30% were achieved in 90% of patients. The side effect profile was consistent with prior clinical trials exploring AA+P in mCRPC. Due to poor accrual, the study was closed prematurely with insufficient sample size for the planned pharmacogenetic analyses.

Conclusion. In this small prospective study terminated for poor accrual, the safety and activity of AA+P in black men with mCRPC was similar to that reported in prior studies exploring AA in largely white populations. Further efforts are needed to address underrepresentation of black men in mCRPC trials.

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Discussion

AA is a steroidal inhibitor of 17α hydroxylase/C17,20-lyase (CYP17), which, in combination with prednisone, is approved for the treatment of mCRPC, based on the results of two randomized phase III trials demonstrating improvements in survival [1, 2]; but black men were largely underrepresented in both. Although poor access to health care is related to inferior outcomes in black men with prostate cancer, at least in part, differences in disease biology may also impact treatment response and survival. Indeed, germline polymorphisms in androgen metabolism genes (AMGs) have been correlated with response to androgen deprivation therapy [3, 4], and several AMG polymorphisms have been demonstrated to be more common in black patients, including polymorphisms in CYP17 [5].

This investigation was designed as a pilot study with a primary objective of determining whether there is a correlation between inherited genetic polymorphisms and antitumor activity (as defined by a decline in PSA level of ≥30%) in black patients with mCRPC treated with abiraterone acetate. Specifically, germline polymorphisms (as determined from baseline peripheral blood samples) in *CYP17* and other genes involved in androgen metabolism were to be evaluated. Because this was the first prospective study, to our knowledge, to explore the relationship of germline polymorphisms in androgen pathway genes with response to hormonal therapy

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in a prospective cohort of black patients with CRPC, the study was designed to be exploratory, hypothesis generating, and to inform the design of larger, more definitive studies.

The primary endpoint of the study was to correlate germline polymorphisms in AMGs to a post-treatment decline in PSA level of ≥30%. Unfortunately, the study was prematurely terminated due to poor accrual, precluding the planned pharmacogenetic analyses. Of 10 evaluable patients treated, 9 had a ≥30% decline in PSA level. Treatment was generally well tolerated, with no subjects discontinuing treatment because of adverse effects. Treatment was generally well tolerated, with no subjects discontinuing treatment because of adverse effects, although incidence of some common adverse effects may have been higher than expected due to small sample size (e.g., fatigue).

To our knowledge, this is the first prospective interventional study exploring a treatment for mCRPC specifically enrolling black men; the study highlights several important lessons. Poor enrollment of black men in prostate cancer clinical trials is likely multifactorial: Black men are more often deemed ineligible for cancer clinical trials and are more likely to refuse participation when eligible [6, 7]. Despite opening our study at two centers with catchment areas made up of a large black population, these factors likely contributed to the poor accrual. Although it did not impact our study, increased use of multinational sites with very small black populations in phase III trials has further exacerbated disparities. Potential solutions include large multicenter postmarketing registries, patient navigation and community education, and dedicated clinical trials enrolling black patients [6, 8]. Although funding for multicenter investigator-initiated studies is often prohibitive, the National Cancer Institute cooperative group system may be an appropriate venue for such studies.

Trial Information	
Disease	Prostate cancer
Stage of disease/treatment	Metastatic/advanced
Prior therapy	No designated number of regimens
Type of study - 1	Phase II
Type of study - 2	Single Arm
Primary Endpoint	Overall response rate
Secondary Endpoint	Efficacy
Secondary Endpoint	Correlative endpoint
Secondary Endpoint	Safety
Additional Details of Endpoints or Study Design	The primary objective of this study was to determine a correlation between inherited genetic polymorphisms and antitumor activity (as defined by a decline in PSA of ≥30%) in black patients with castration-resistant prostate cancer treated with abiraterone acetate. Specifically, germline polymorphisms (as determined from baseline peripheral blood samples) in *CYP17* and other genes involved in androgen metabolism will be evaluated—a total of approximately 120 polymorphisms tagging all known, common variations across 20 genes of interest. Unfortunately, the study was prematurely terminated due to poor accrual, precluding the planned pharmacogenetic analyses. Of 10 evaluable patients treated, 9 had a ≥30% PSA decline.
Investigator's Analysis	Active but results overtaken by other developments

Drug Information	
Drug 1	
Generic/Working name	Abiraterone acetate
Trade name	Zytiga
Company name	Janssen Biotech
Drug type	Biological
Drug class	Androgen receptor
Dose	1,000 mg per flat dose
Route	Oral
Schedule of Administration	Take 1,000 mg every morning on an empty stomach
Drug 2	
Generic/Working name	Prednisone
Drug class	Corticosteroid
Dose	5 mg, twice daily, per flat dose
Route	Oral

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Patient Characteristics	
Number of patients, male	11
Number of patients, female	0
Stage	Stage IV, castration-resistant prostate cancer
Age	Median (range): 66 (54–78)
Number of prior systemic therapies	Median (range): 3 (1–4)
Performance Status: ECOG	0 — 8 1 — 3 2 — 3 — Unknown —
Cancer Types or Histologic Subtypes	Adenocarcinoma of the prostate 11

Primary Assessment Method	
Control Arm: Adenocarcinoma of the Prostate	
Number of patients screened	11
Number of patients enrolled	11
Number of patients evaluable for toxicity	10
Number of patients evaluated for efficacy	10
Response assessment PR	*n* = 9 (90)
Response assessment SD	*n* = 1 (10)
Control Arm: Total Patient Population	
Number of patients screened	11
Number of patients enrolled	11
Number of patients evaluable for toxicity	10
Number of patients evaluated for efficacy	10
Response assessment PR	*n* = 9 (90)
Response assessment SD	*n* = 1 (10)

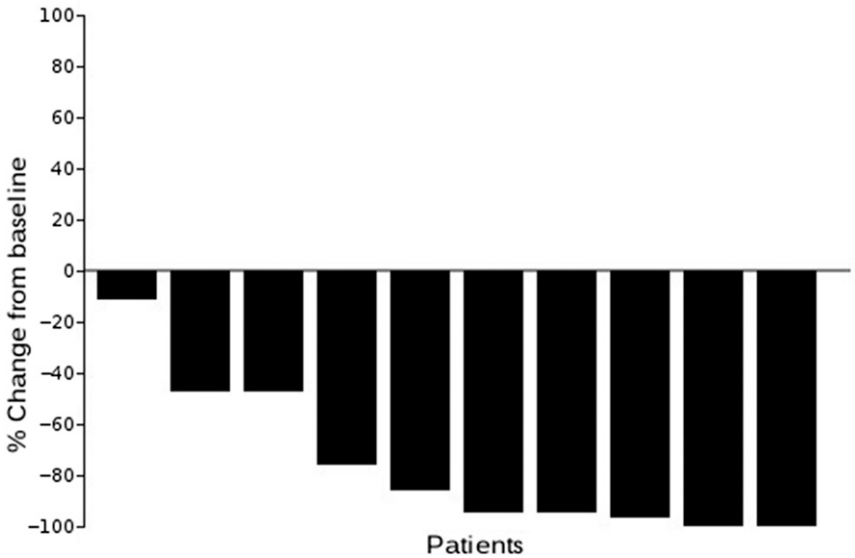

Figure 1. Waterfall plot of maximum post-treatment declines in prostate-specific antigen levels.

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Adverse Events

All Cycles							
Name	***NC/NA**	**1**	**2**	**3**	**4**	**5**	**All Grades**
Fatigue	30%	40%	30%	0%	0%	0%	70%
Hot flashes	60%	30%	10%	0%	0%	0%	40%
Nausea	60%	40%	0%	0%	0%	0%	40%
Vomiting	60%	40%	0%	0%	0%	0%	40%
Hypocalcemia	80%	0%	10%	10%	0%	0%	20%
Hypokalemia	80%	10%	0%	10%	0%	0%	20%
Cough	70%	30%	0%	0%	0%	0%	30%
Alkaline phosphatase level increased	30%	50%	10%	10%	0%	0%	70%
Hypophosphatemia	60%	10%	20%	10%	0%	0%	40%
Urinary incontinence	70%	20%	10%	0%	0%	0%	30%
Platelet count decreased	80%	20%	0%	0%	0%	0%	20%
Hyperglycemia	50%	40%	10%	0%	0%	0%	50%
Diarrhea	80%	20%	0%	0%	0%	0%	20%
Lymphocyte count decreased	60%	10%	20%	10%	0%	0%	40%
Anorexia	70%	10%	20%	0%	0%	0%	30%
Muscle weakness in lower limb	80%	10%	0%	10%	0%	0%	20%
Hypoalbuminemia	80%	0%	20%	0%	0%	0%	20%
Aspartate aminotransferase level increased	70%	30%	0%	0%	0%	0%	30%
Alanine aminotransferase level increased	80%	20%	0%	0%	0%	0%	20%
Back pain	70%	30%	0%	0%	0%	0%	30%

Adverse Events Legend
>1 occurrence in any individual patient.
*No Change from Baseline/No Adverse Event.

Assessment, Analysis, and Discussion

Completion	Study terminated before completion
Terminated reason	Did not fully accrue
Pharmacokinetics/Pharmacodynamics	Not collected
Investigator's Assessment	Endpoint not met because study closed early due to poor accrual.

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This investigation was designed as a pilot study with a primary objective of determining whether there is a correlation between inherited genetic polymorphisms and antitumor activity (as defined by a $\geq$30% decline in prostate-specific antigen [PSA] level) in black patients with mCRPC treated with abiraterone acetate. Specifically, germline polymorphisms (as determined from baseline peripheral blood samples) in CYP17 and other genes involved in androgen metabolism were to be evaluated. Because this was the first prospective study, to our knowledge, to explore the relationship of germline polymorphisms in androgen pathway genes with response to hormonal therapy in a prospective cohort of black patients with CRPC, the study was designed to be exploratory, hypothesis generating, and to inform the design of larger more definitive studies.

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likely multifactorial: Black men are more often deemed ineligible for cancer clinical trials and are more likely to refuse participation when eligible [6, 7]. Despite opening our study at two centers with catchment areas made up of a large black population, these factors likely contributed to the poor accrual. Although it did not impact our study, increased use of multinational sites with very small black populations in phase III trials has further exacerbated disparities. Potential solutions include large multicenter postmarketing registries, patient navigation and community education, and dedicated clinical trials enrolling black patients [6, 8]. Although funding for multicenter investigator-initiated studies is often prohibitive, the National Cancer Institute cooperative group system may be an appropriate venue for such studies.

Disclosures

Che-Kai Tsao: Dendreon (C/A, RF); **Bobby Liaw:** Bayer (C/A); **William Kyu Oh:** Janssen (C/A); **Matthew David Galsky:** Genentech, AstraZeneca, Astellas (C/A), Bristol-Myers Squibb, Merck, Dendreon (RF), Dual Therapeutics (OI). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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